Loss-of-function mutations in the trace amine-associated receptor 1 (TAAR1) among patients with major mental disorders

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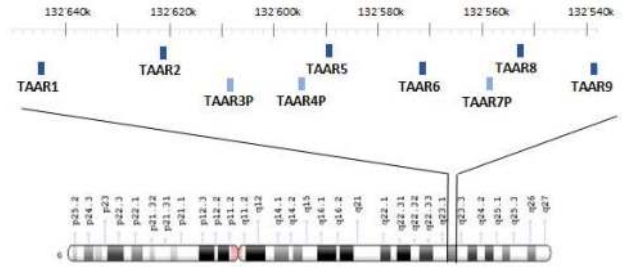
Objectives

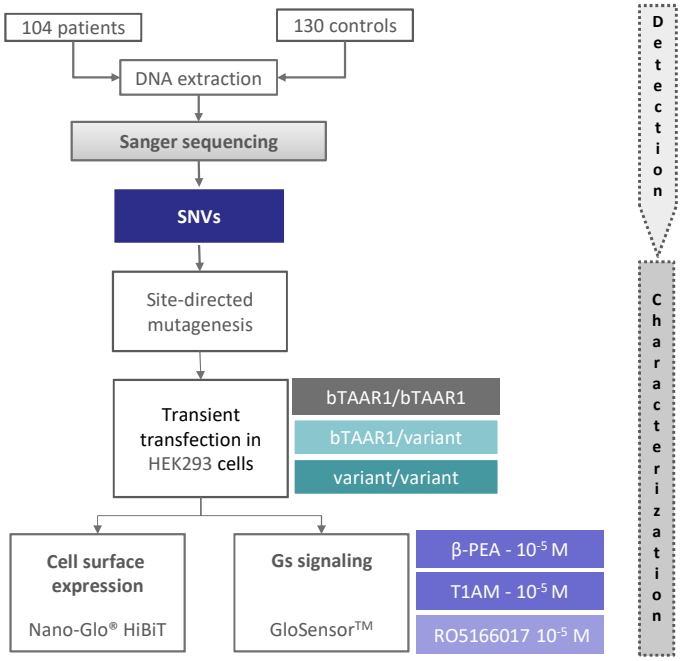
To identify and functionally characterize variants in the trace amine associated receptor 1 (**TAAR1**) in a cohort of patients suffering from **major mental disorders**.

Background

The G protein-coupled receptor (GPCR) TAAR1 is widely expressed across brain areas involved in **emotions**, **reward** and **cognition**, and modulates monoaminergic and glutamatergic neurotransmission. The human gene for TAAR1 maps to locus **6q23**, within a region associated to major mental disorders.



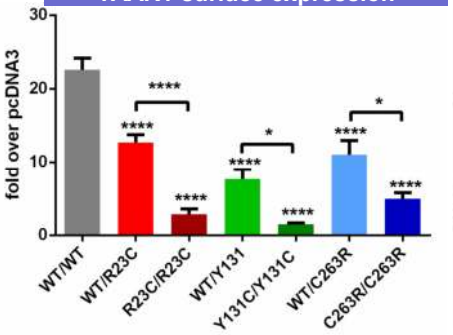
Materials & Methods



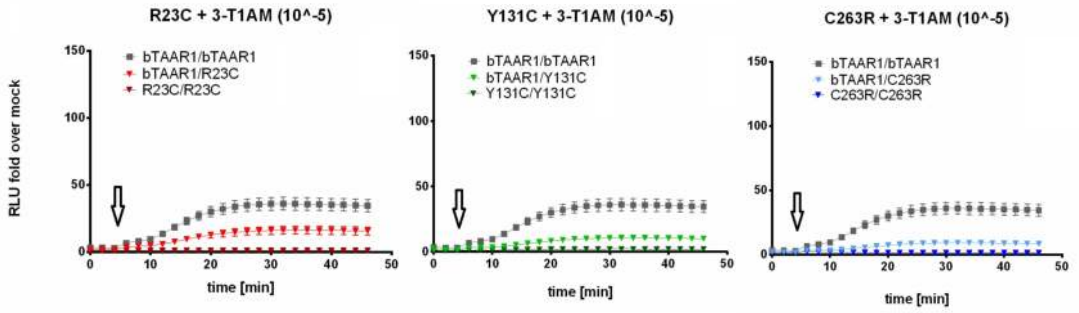
Results

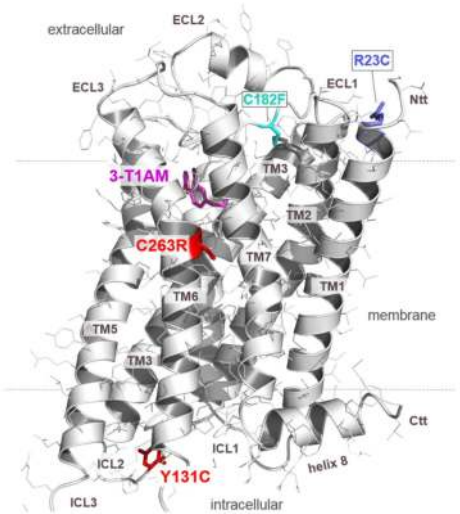
We detected **13 missense variants**, with a significant enrichment in patients as compared to healthy controls. In cells co-trasfected with TAAR1-wild-type and TAAR1-variants - **R23C**, **Y131C**, **C263R** - we showed:

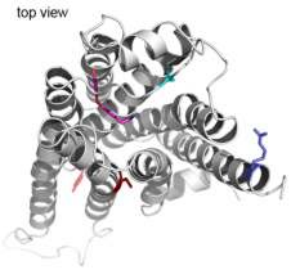
(1) Significantly reduced TAAR1 surface expression



(2) Dampened TAAR1-initiated $G_{\alpha s}$ signaling in response to every tested ligand.







Homology model of human TAAR1 bound with T1AM

R23C, Y131C, and C263R map to functionally important highly conserved positions across TAAR1 orthologous and paralogous genes.

Conclusions

Our findings suggest that disruptions of TAAR1 activity may be relevant to the pathophysiology of mental disorders, thereby providing a promising target for novel psychopharmacological interventions.